Remarks

Claims Pending in the Application

Claim 15 has been amended. Claims 4, 5, 10-13, and 15 remain pending in this application.

Examiner's Rejection of Claim 10 as Obvious over Myers

The Examiner's rejection of Claim 10 as obvious over Myers is a newly presented rejection, in contrast to the Examiner's comments: See page 3, last paragraph of the final action, where the Examiner states ". . . therefore, the rejection of Claim 10, as being obvious in view of the Myers et al. reference, is maintained and Claim 15 is rejected." Applicant submits the rejection of Claim 10 as obvious in view of Myers is newly presented in this final action. Previously, Myers et al. had been cited only against Claim 10 in an anticipation (Section 102) rejection.

According to MPP Section 706.07(A), a second action on the merits shall be final, *except where the Examiner introduces a new ground of rejection that is neither necessitated by applicant's Amendment of the claims nor based on information submitted in an Information Disclosure Statement filed during the period as set forth in 37 C.F.R. Section 1.97(c).* Applicant's submit the 103 rejection of Claim 10 as being obvious in view of the Myers et al. reference is newly presented in the final office action. Accordingly, Applicants respectfully request that the premature finality of this action be withdrawn.

Furthermore, Applicants respectfully traverse the Examiner's obviousness rejection over the Myers reference. The Examiner cites Myers as teaching the use of quinazoline compounds

as inhibitory agents in the treatment of protein tyrosine kinase-regulated diseases. The Examiner asserts JAK-3 is a species of tyrosine kinase and that Myers teaches "fine-tuning selectivity versus other tyrosine kinases is possible using quinazoline as a template".

Inhibition of c-jun is disclosed in the applicant's specification as accomplished by inhibiting JAK-3 (and not by inhibiting other protein tyrosine kinases such as BTK, SYK, and LYN). This selected inhibition of c-jun by JAK-3 inhibition, and the failure of other protein tyrosine kinase inhibition to alter c-jun expression, distinguishes Applicants' invention from the prior art.

As characterized by the Examiner, Myers *suggests* that the inhibition of *any* protein tyrosine kinase would be expected to inhibit activation of c-jun and any consequent downstream activity. However, the reference fails to associate c-jun inhibition with inhibition of any specific protein kinase. Moreover, Applicants' data clearly teaches this is not the case.

As shown in Example 1, at pages 21-25 of Applicant's specification, specific inhibition of JAK-3 resulted in inhibition of c-jun expression. In contrast, inhibition of BTK, SYK, or LYN kinase failed to impact *c-jun* expression. Applicants submit the instant specification is the first to link specific JAK-3 inhibition with c-jun inhibition. Nothing in the cited Myers reference teaches or suggests the selective inhibition of c-jun expression by inhibiting JAK-3 kinase.

Because Claim 10 recites a method for specifically inhibiting c-jun expression using quinazoline compounds that are selective JAK-3 inhibitors, claim 10 cannot be considered obvious over the cited reference. Removal of this rejection is requested.

B

Examiner's Rejection of Claims 4-5, 11-13, and 15 as Obvious Over the Combination of Karin, Riedy, Rosette and Karin, and Chae

Claims 4-5, 11-13, and 15 have been rejected as obvious over the combination of Karin, Riedy, Rosette and Karin, and Chae. Applicants respectfully traverse this rejection.

Karin is cited for teaching a role of c-jun and c-fos (activating proteins) in apoptosis. Jun amino terminal kinases (JNK) are cited as essential for induction of apoptosis via c-jun transcription. The Examiner notes the primary reference does not teach the use of a specific inhibitory compound of JAK-3 as a means of inhibiting c-jun activation.

Applicants submit the primary reference fails to teach or suggest the use of a JAK-3 inhibitor to specifically inhibit c-jun. In particular, JAK-3 inhibitory quinazoline compounds of the dependent claims are not taught or suggested as a means for specifically inhibiting c-jun activation. None of the secondary references, alone or in combination address this deficiency of the primary reference.

Riedy is cited as teaching activation of JAK-3 by cytokines in B cells. Rosette and Karin are cited for teaching that tyrosine kinase inhibitors block c-jun induction by UV light. Chae is cited as teaching protein tyrosine kinase activation in radiation-induced activation of c-jun.

According to the Examiner, it would be obvious to one of ordinary skill in the art to utilize a JAK-3 inhibitor to prevent the activation of c-jun in response to cellular stress. The Examiner states as his basis, that "the literature demonstrates that JAK activation, and in particular JAK-3, precedes and has regulatory power over the induction of c-jun protooncogene expression". (Page 5, last paragraph). Applicants specifically disagree with the Examiner's characterization of the prior art. None of the cited references, alone or in combination, make the leap of logic that is asserted by the Examiner. There is no demonstration in the cited references

that JAK activation, and in particular JAK-3 activation, precedes and has regulatory power over the induction of c-jun expression. The Applicants request the Examiner provide a more specific citation for this statement or remove it from his rejection of the claims.

Because the references, alone or in combination, fail to teach or suggest the invention as claimed, Applicants respectfully request removal of this rejection.

Examiner's Rejection of Claim 10 as Obvious Over the Combination of Karin, Riedy, Rosette and Karin, Chae, Myers, Narla, and Leonard.

Claim 10 has been rejected as obvious over the combination of Karin, Riedy, Rosette and Karin, Chae, Myers, Narla, and Leonard. Applicants respectfully traverse this rejection.

The Examiner makes this seven-reference obviousness rejection, using Karin et al. as a primary reference. As discussed in the prior obviousness rejection, Karin et al. is cited as teaching c-jun as a transcription factor, its cooperation with the transcription factor c-fos, and the relationship of these factors to specific diseases as well as activation of p38 and jun amino terminal kinases (JNK). The Examiner again notes that Karin et al. does not indicate use of a compound that inhibits JAK-3 specifically, but finds it "would have been obvious to one of ordinary skill in the art to have modified the teachings in Karin et al. because utilizing a compound known to inhibit JAK-3 would clarify the exact role JAK-3 plays in the overall cascade by elucidating what downstream factors are being regulated by JAK-3. Thus, yielding a greater understanding of the entire process necessary in formulating methods of inhibiting cell apoptosis." (Page 6, last paragraph).

Myers et al. is cited as teaching the inhibitory effects of quinazoline-based compounds on several species of tyrosine kinases. In particular, Myers teaches use of 6,7-

dimethoxyquinazoline, testing a myriad of different moieties at different positions. The Examiner asserts "Thus, it would have been clearly anticipated to take the teachings of Myers et al. and further fine tune the compound and test its effectiveness against other members of the genus of tyrosine kinases." The Examiner summarizes this information by stating "Therefore the use of quinazolines to inhibit tyrosine kinases, including JAK-3, is taught in Myers et al." In contrast to the Examiner's statement, nothing in Myers et al. teaches or suggests specific quinazolines useful for specific inhibition of JAK-3, as claimed.

Narla is cited as teaching specific quinazoline compounds as inhibitors of EGF-R tyrosine kinase. Leonard is cited as teaching that the identification of compounds that inhibit JAK-Stat signaling pathway would be useful in treating disorders controlled or impacted by the pathway. Chae is cited as teaching a nexus within the biochemical cascade between upstream tyrosine kinase activation and downstream c-jun. The Examiner combines these seven references to find it would have been obvious to one of ordinary skill in the art to take the teachings of Karin et al. and incorporate Chae et al. and Myers et al. together with the known inhibitors of JAK-3. Applicants respectfully traverse this rejection.

As stated above, the primary reference, Karin et al., makes no connection between inhibition of JAK-3 kinase and specific inhibition of c-jun expression. Nothing in the cited references, alone or in combination rectifies this deficiency of the primary reference.

As discussed above, none of the references, alone or in combination teaches or suggests the specific inhibition of c-jun expression is mediated by JAK-3 inhibition. In contrast, the prior art references fail to distinguish between specific tyrosine kinases and their role in activating c-jun. While a non-specific protein tyrosine kinase inhibitor such as genestein has been demonstrated by Applicants to inhibit c-jun activation, such broad spectrum tyrosine kinase

inhibitors also inhibit other tyrosine kinase mediated events. In contrast, Applicants' recognition that c-jun expression can be specifically inhibited by JAK-3 inhibitors, and not by specific inhibitors of BTK, SYK, and LYN kinase is not predicted from the art. Such selective inhibition of c-jun expression is particularly useful for administration of complex systems. Because the cited combination fails to teach or suggest the invention as claimed, Applicants respectfully request removal of this obviousness rejection.

In view of the foregoing Amendment and Remarks, Applicants assert the claims are in condition for issuance.

If all issues are not resolved to the Examiner's satisfaction by this Amendment, Applicants request that the Examiner direct questions and comments to the Applicant's representative by telephone at the number indicated below.

Respectfully submitted,

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